

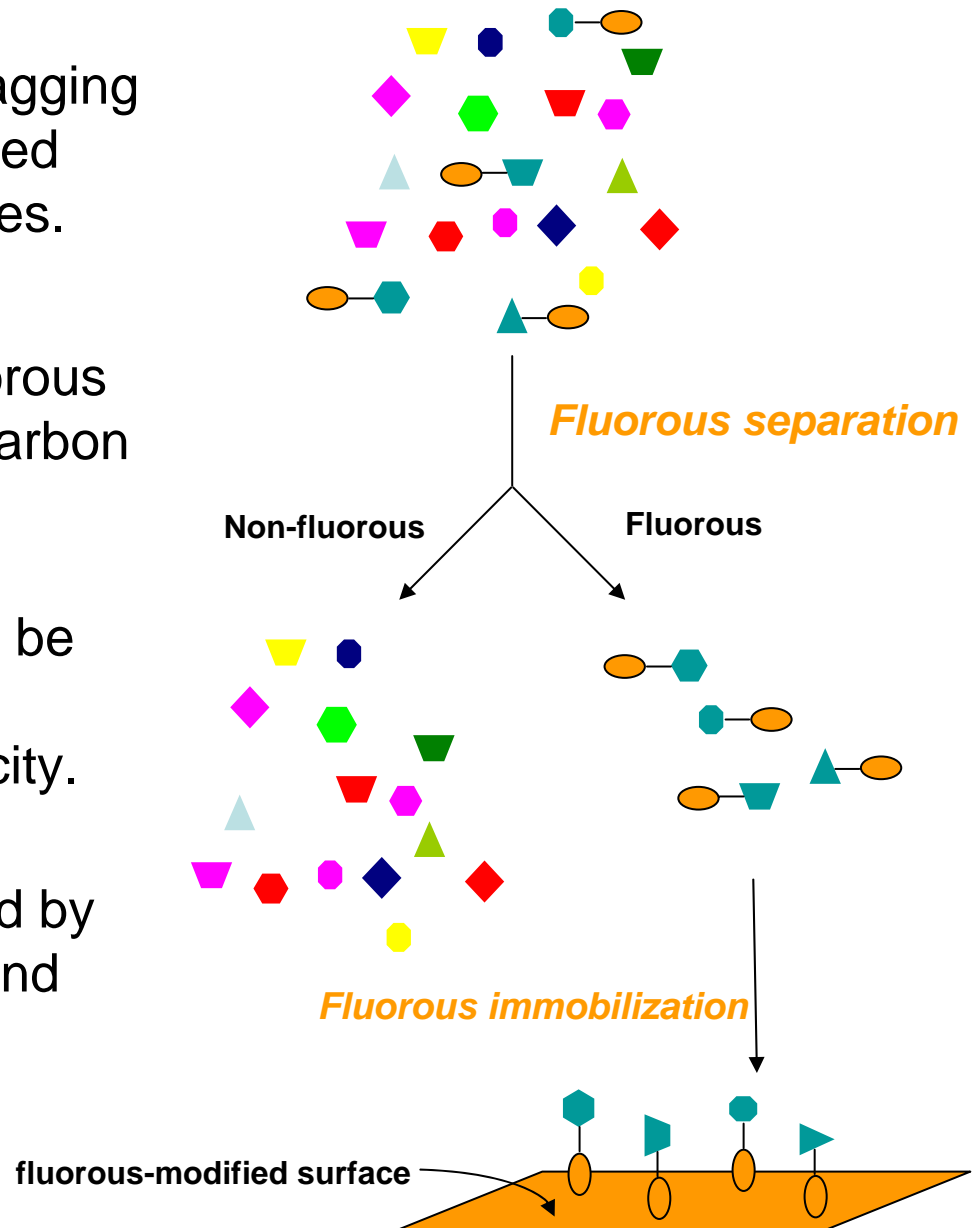
Fluorous Techniques in Small Molecule Synthesis



- Fluorous separation techniques
 - Solid-phase extraction (SPE)
 - Flash chromatography
 - Chromatography (HPLC)
- Combinatorial synthesis
 - Microwave reactions
 - Multicomponent reactions (MCR)
 - Parallel synthesis
 - Diversity-oriented synthesis (DOS)
 - Fluorous Mixture synthesis (FMS)

What is Fluorous Technology?

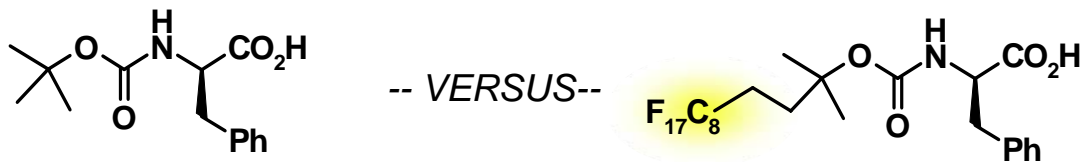
- Fluorous chemistry is a novel tagging technology that separates desired molecules from complex mixtures.
- Molecules can be rendered fluorous by the attachment of perfluorocarbon domains.
- Fluorous tagged molecules can be separated from non-fluorous molecules exploiting fluorophilicity.
- Fluorous techniques are marked by high selectivity, low reactivity, and exceptional breadth



Compounds with permanent fluorinated domains (e.g. reagents):

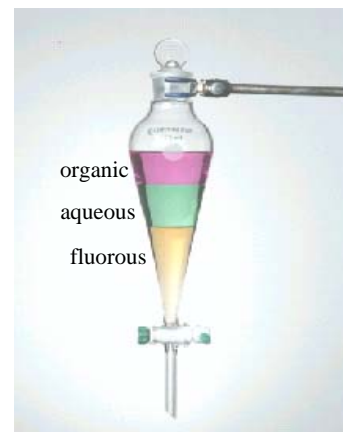


Compounds with temporary fluororous tags (e.g. substrates):



■ Liquid-Liquid Extraction

- “Heavy” fluorous technique
- Generally requires large F content, ~60%



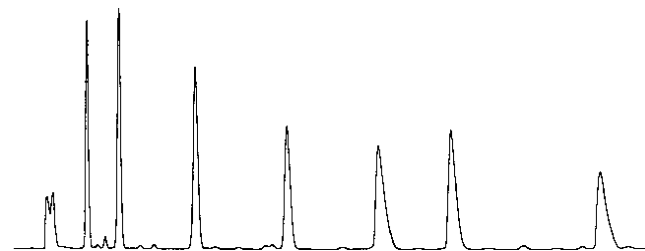
■ Fluorous Solid Phase Extraction (F-SPE)

- “Light” fluorous technique
- Separates fluorous from non-fluorous
- No fluorous solvents used

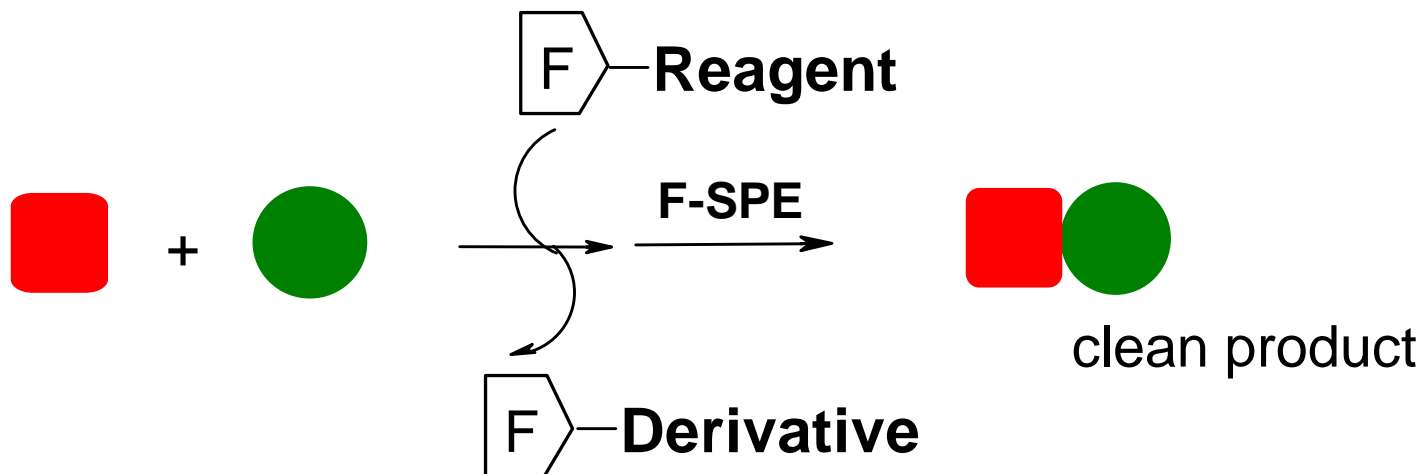


■ Fluorous Chromatography (F-HPLC)

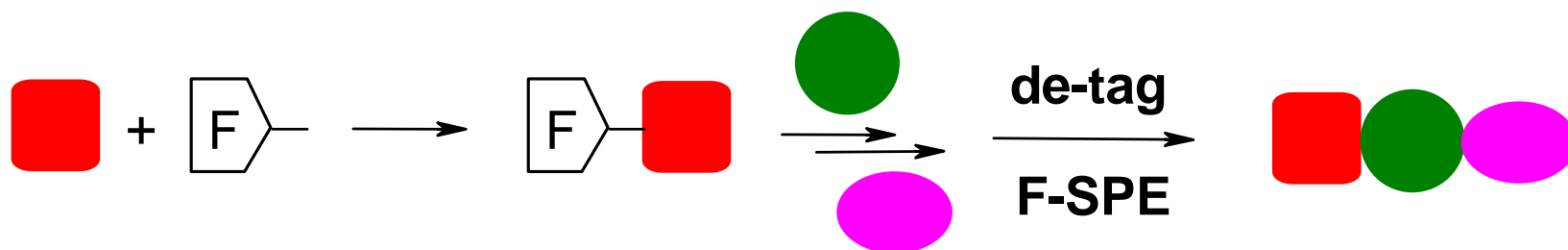
- Separates fluorous from fluorous
- More fluorous = Greater retention



- *Tagging reagents/scavengers/catalysts*



- *Tagging substrates for parallel and mixture syntheses*

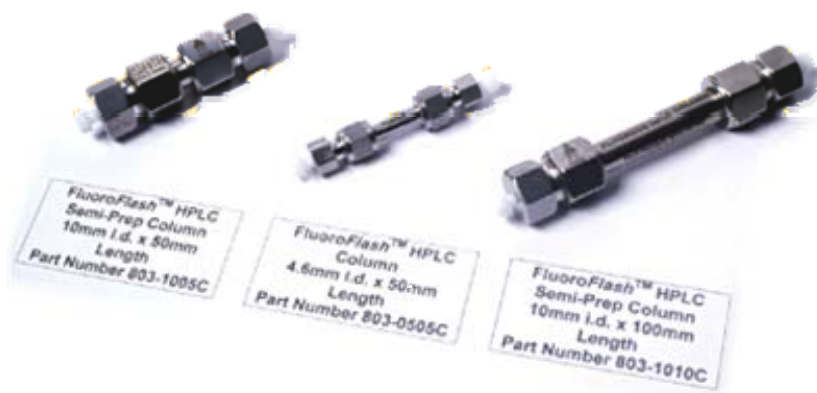




SPE Cartridges



Flash Columns and Samplets



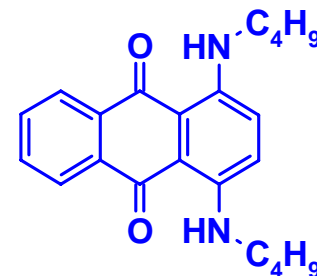
HPLC Columns



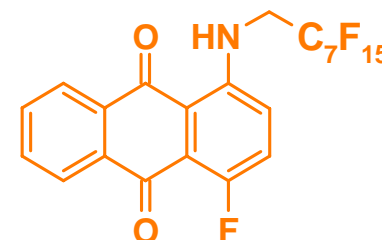
TLC Plates



Bulk Silica



organic dye (blue)



fluorous dye (orange)

Left tube: beginning of fluorophobic wash (80:20 MeOH:H₂O)

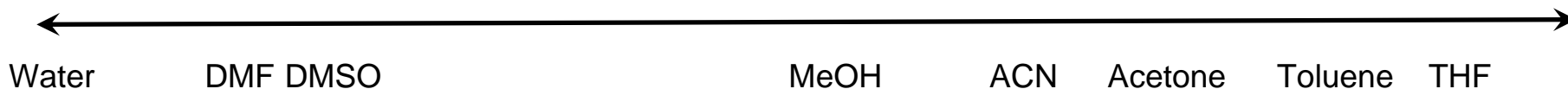
Center tube: end of fluorophobic wash

Right tube: end of fluorophilic wash (100% MeOH)

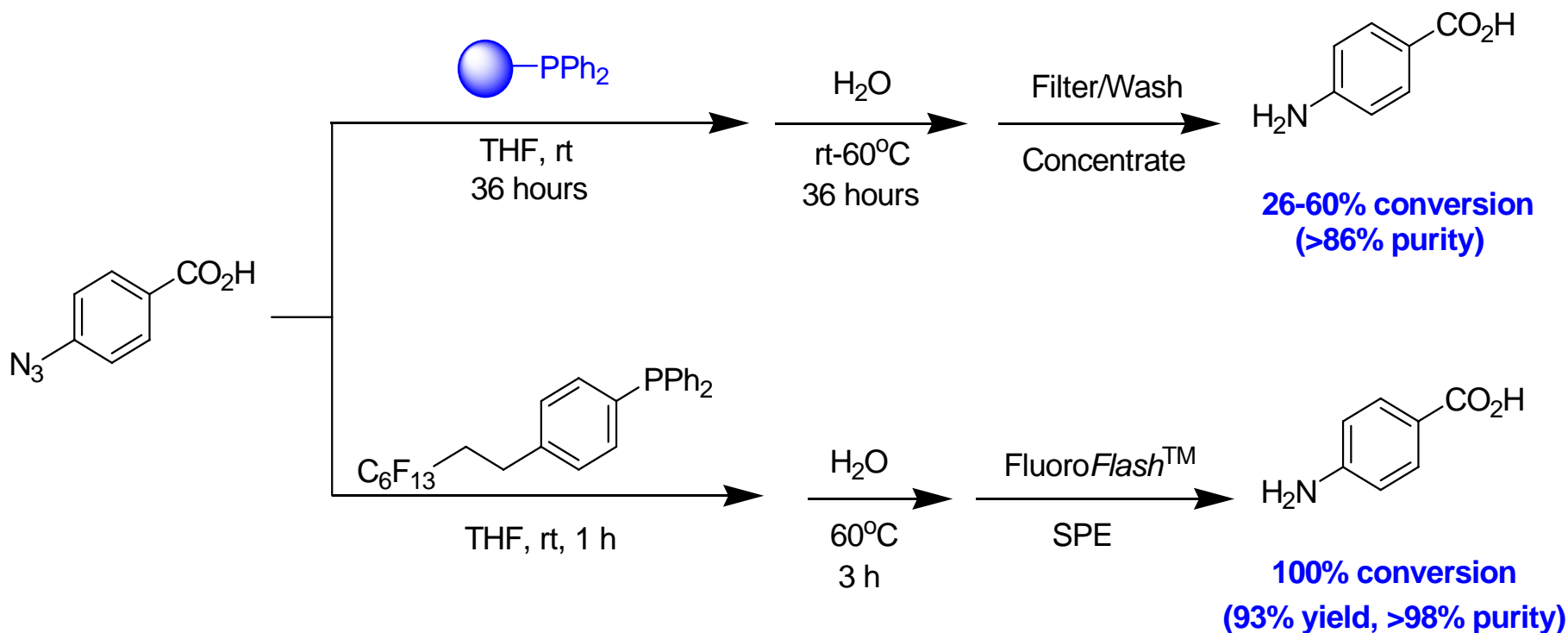
Fluorophobic

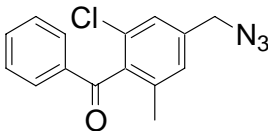
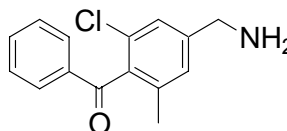
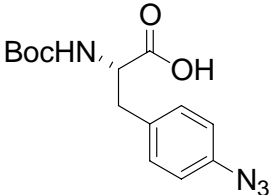
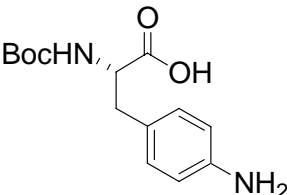
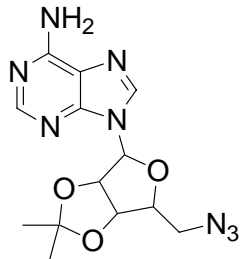
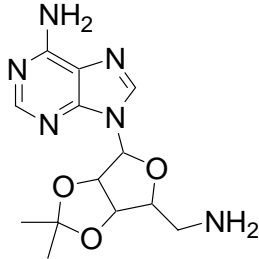
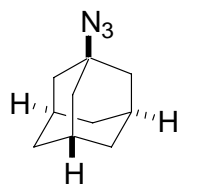
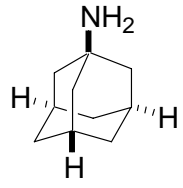
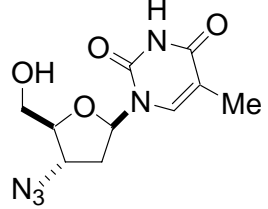
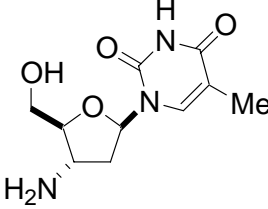
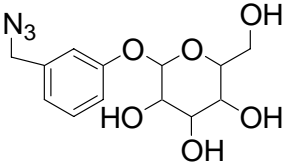
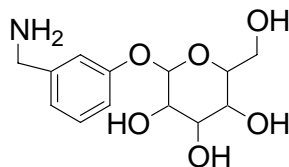
Typical Solvents for F-SPE

Fluorophilic



Fluorous/Resin-PPh₃ Comparison



entry	RN ₃	RNH ₂	yield (%)	purity (%)
1			86	98/95
2			91	98/95
3			88	98/95
4			92	98/95
5			82	95/92
6			80	97/93

24-Channel Plates



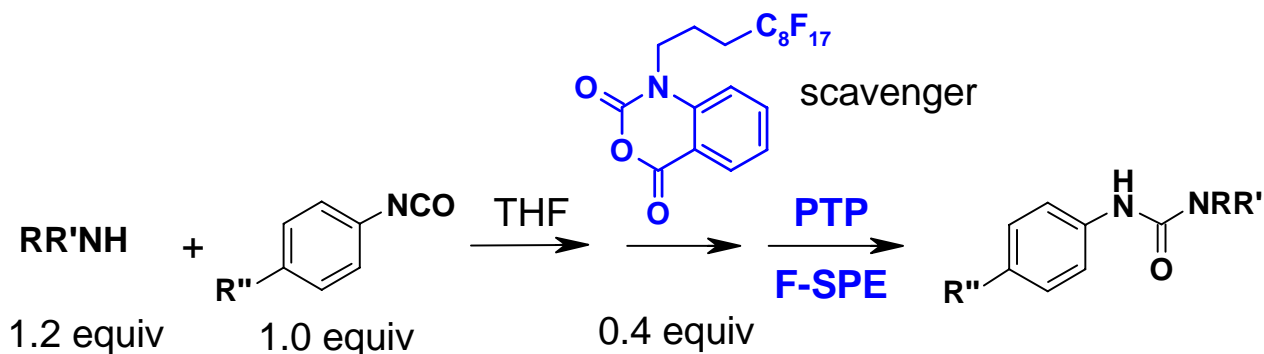
- 3-4 g F-silica gel
- 10 mL receiving well
- 10-100 mg product purification
- plate concentration by Genevac
- vacuum or gravity SPE

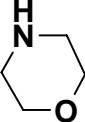
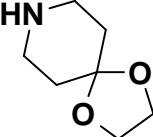
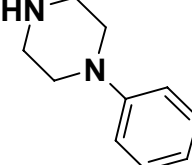
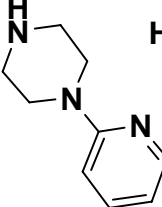
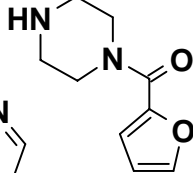
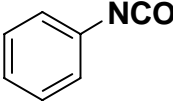
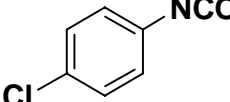
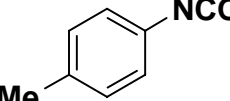
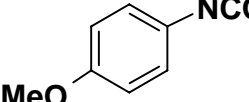
96-Well Ex-Block



- up to 1.5 g of F-silica gel
- 3 mL receiving well
- use large size (100 μm) silica
- gravity SPE
- plate can be reused

PTP F-SPE for Scavenging Reactions

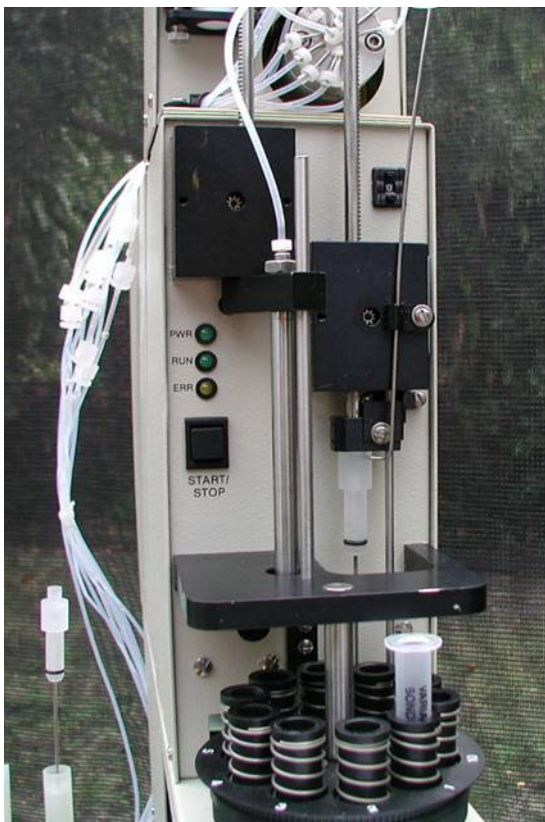


	H_2NBu					
	95(92)*	83(96)	95(93)	86(96)	92(91)	100(96)
	83(100)	81(99)	79(100)	81(100)	83(100)	90(100)
	100(80)	100(96)	100(97)	100(94)	100(96)	100(99)
	100(94)	100(99)	100(100)	100(100)	100(100)	100(100)

* yield% (purity%, UV254)

yield 79-100%, product purity >90% (one exception)

Caliper Life Sciences (formerly Zymark Corp)



Single unit (10 Cartridges)



10 units parallel (10x10 cartridges)

- **Automatic sample loading (including samples containing suspended solids)**
- **Pump-controlled solvent delivery system with a choice of 8 solvents**
- **Automatically conditions, rinses and elutes cartridges**
- **10 Cartridges sequential, up to 10 modules parallel and controlled by a PC**

Large Scale Flash Chromatography

variable cartridge size, gradient solvent, UV-triggered fraction collection



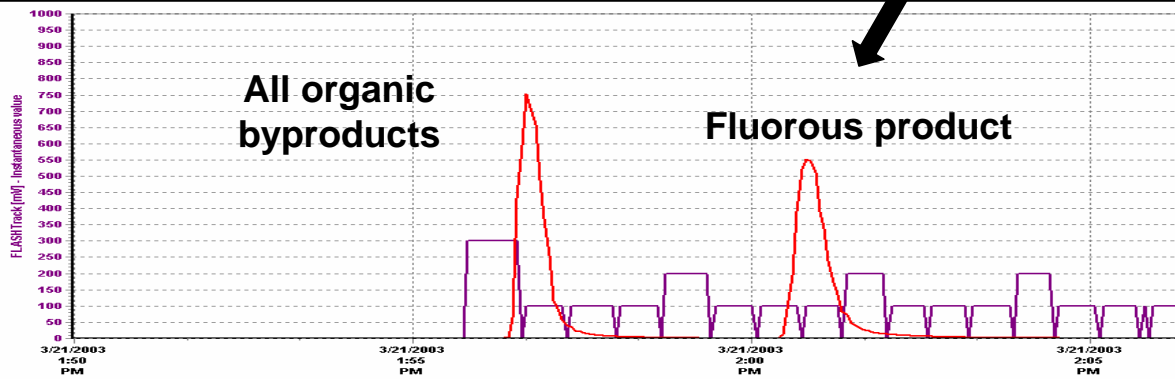
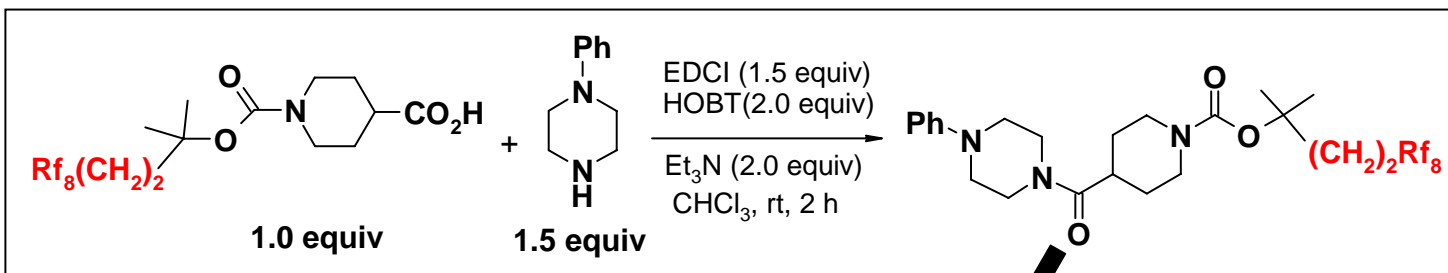
ISCO



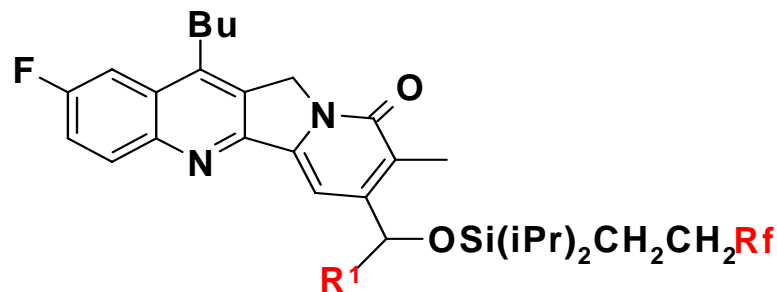
Biotage



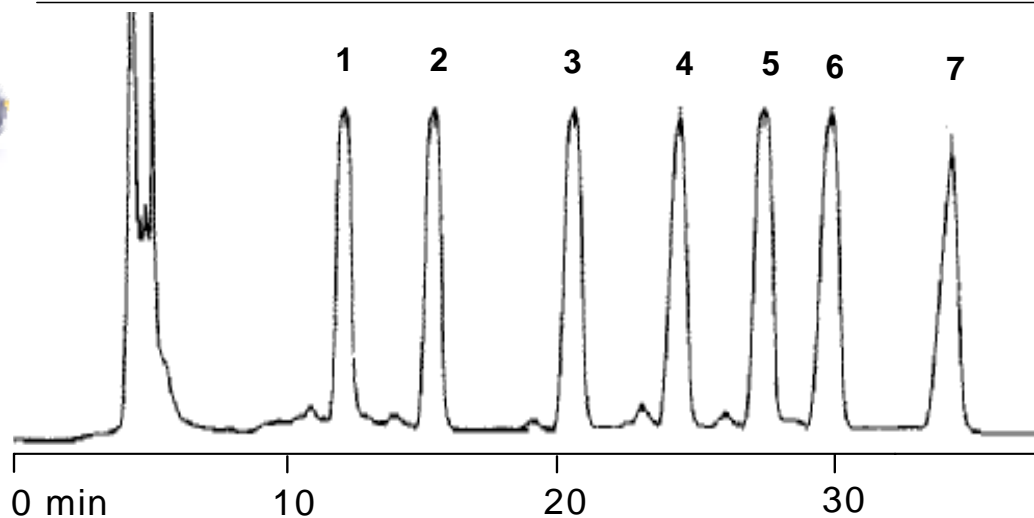
FlashMaster II



Fluorous HPLC for Demixing



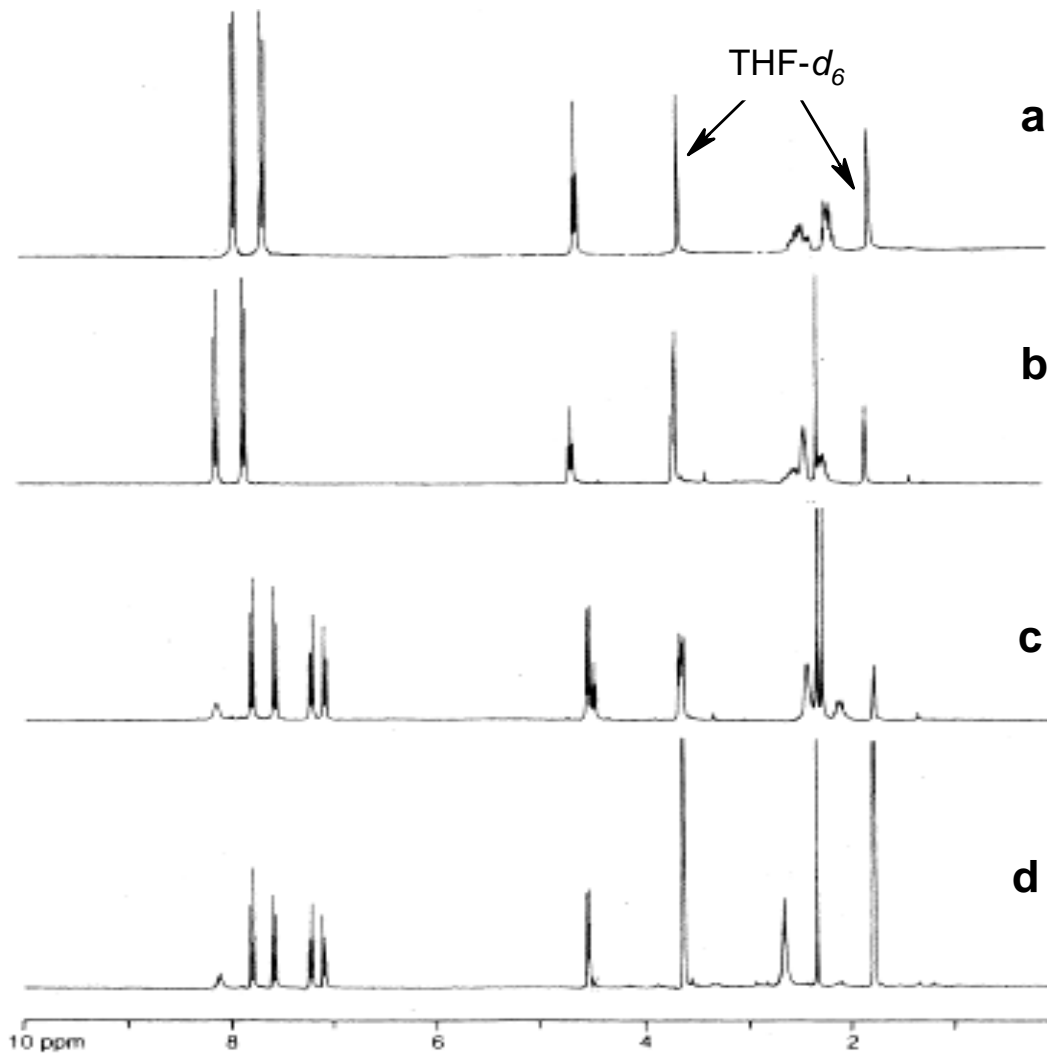
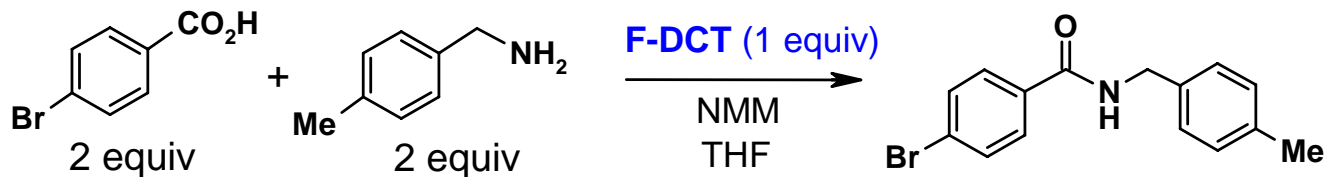
	1	2	3	4	5	6	7
R_f	C ₃ F ₇	C ₄ F ₉	C ₆ F ₁₀	C ₇ F ₁₅	C ₈ F ₁₇	C ₉ F ₁₉	C ₁₀ F ₂₁
R₁	Me	Pr	Et	s-Bu	<i>i</i> -Pr	<i>c</i> -C ₆ H ₁₁	CH ₂ CH ₂ - <i>c</i> -C ₆ H ₁₁



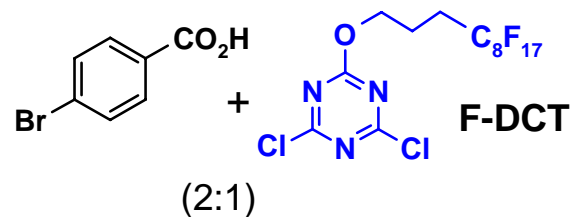
F-HPLC column (20 x 250 mm, 5 mm), gradient 88:12 MeOH-H₂O to 100% MeOH in 28 min, then to 100% THF in 7 min, 12 mL/min

Separation fluorous mixture based on fluorine content

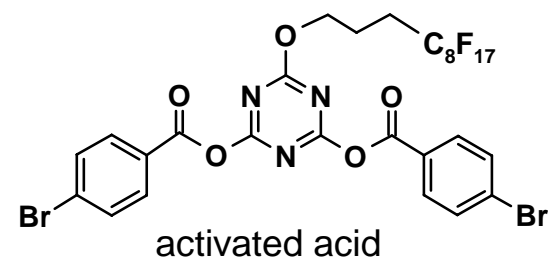
- 1) **Solution-phase** reaction kinetics
- 2) Easy adaptation of literature procedures, **short method development time**
- 3) Easy **reaction monitoring** by common analytical methods (TLC, HPLC, IR and NMR)
- 4) **Separation** by fluorous methods as well as conventional methods (distillation, crystallization and chromatography)
- 5) Light fluorous molecules soluble in many organic solvents, **no fluorous solvents** for reactions and separations
- 6) **More than one fluorous reagent** possible for a single reaction
- 7) Good **“combinatorial” capability** with existing technologies (microwave, microarray, MCR, DOS, SPS....)
- 8) **Recover** fluorous materials after separation



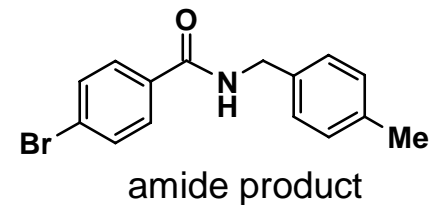
a



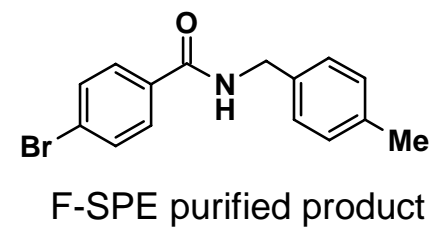
b



c



d





MW Reactor

fluorous compounds are stable under μW irradiation

+



Plate to Plate F-SPE

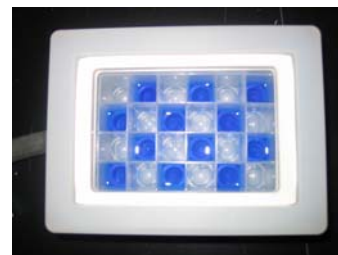
for parallel separation

+

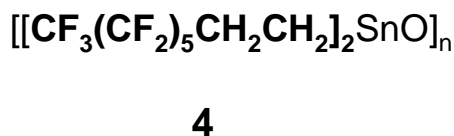
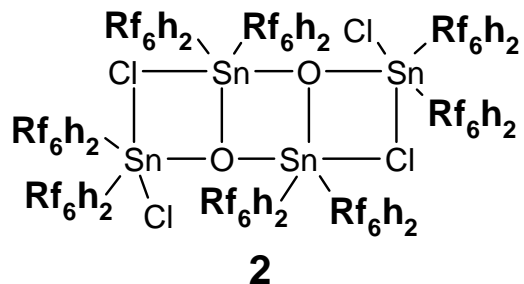
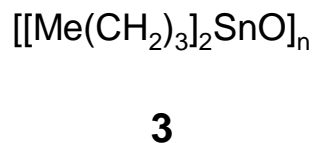
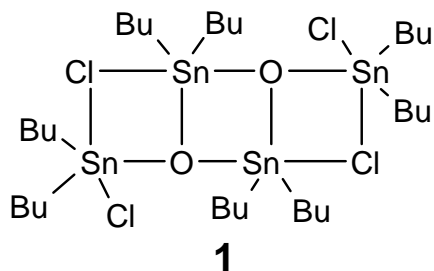
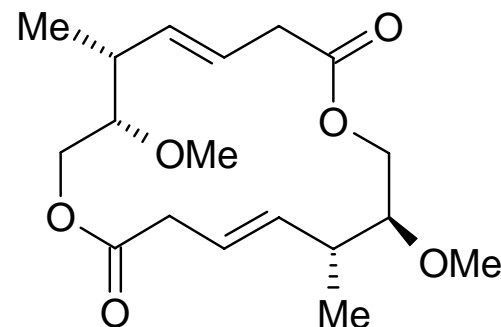
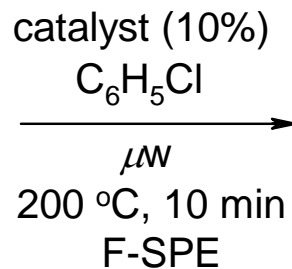
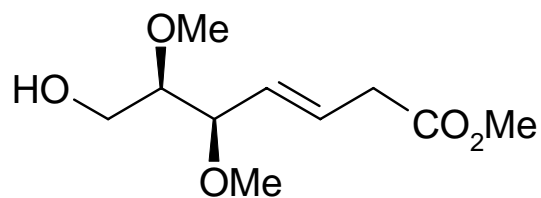


SpeedVac

for concentration of SPE receiving plates

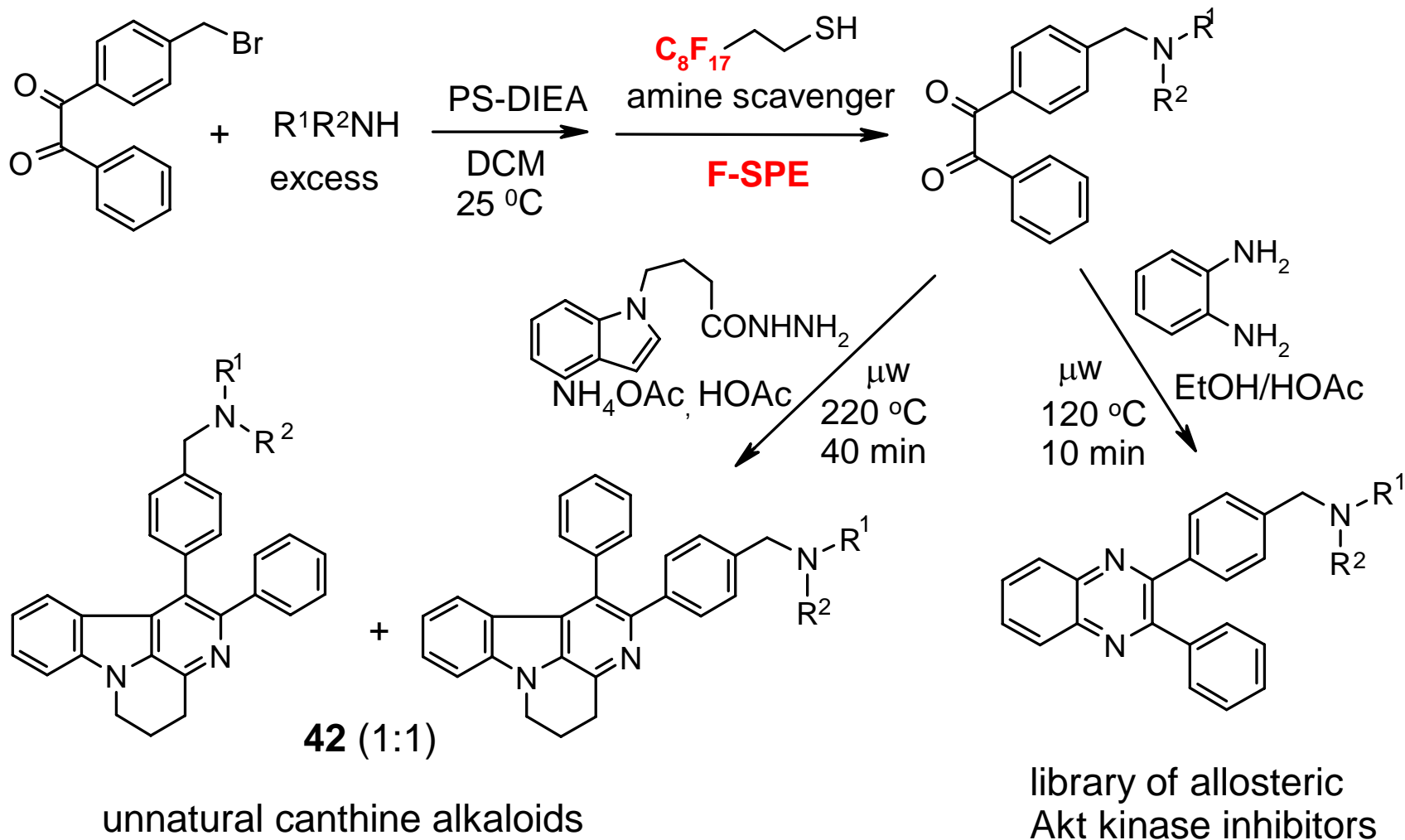


F-Tin Oxide for Transesterifications

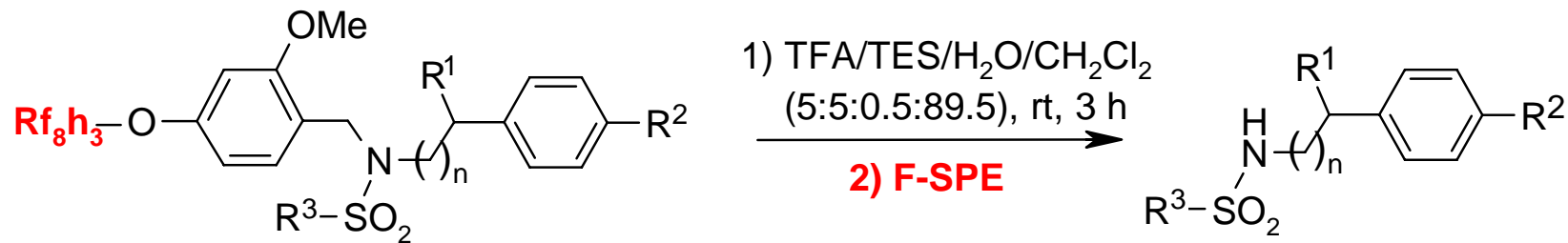
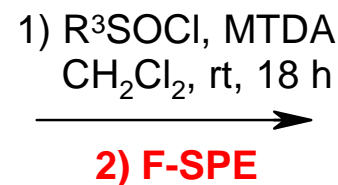
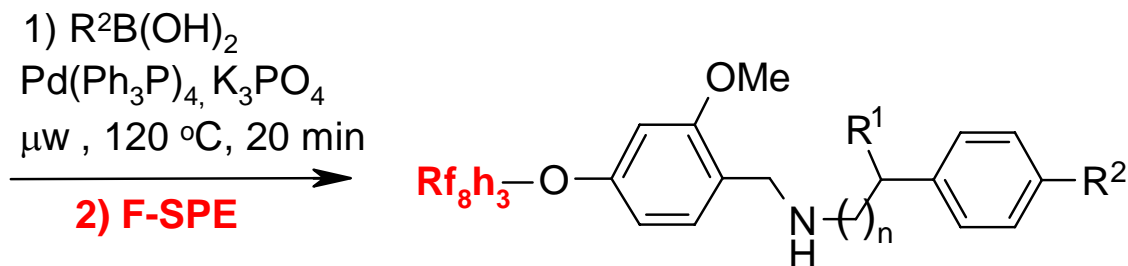
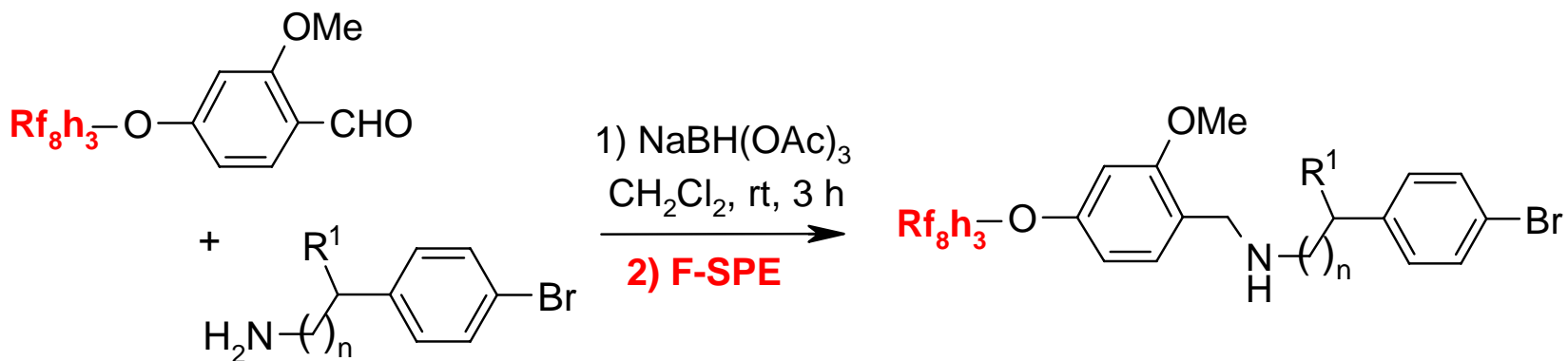


catalyst	yield
1	60%
2	78%
3	27%
4	80%

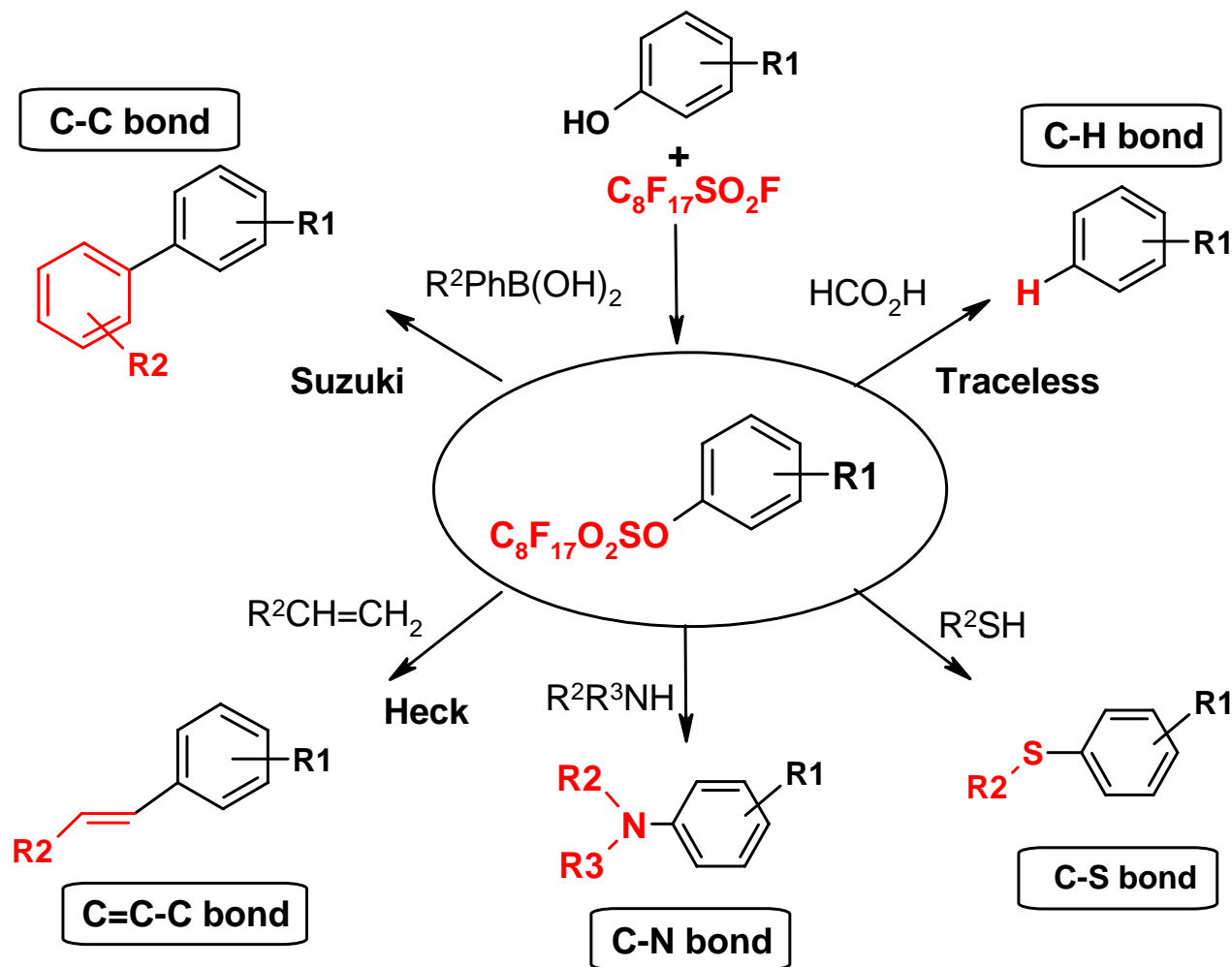
F-catalyst 4 has the best result



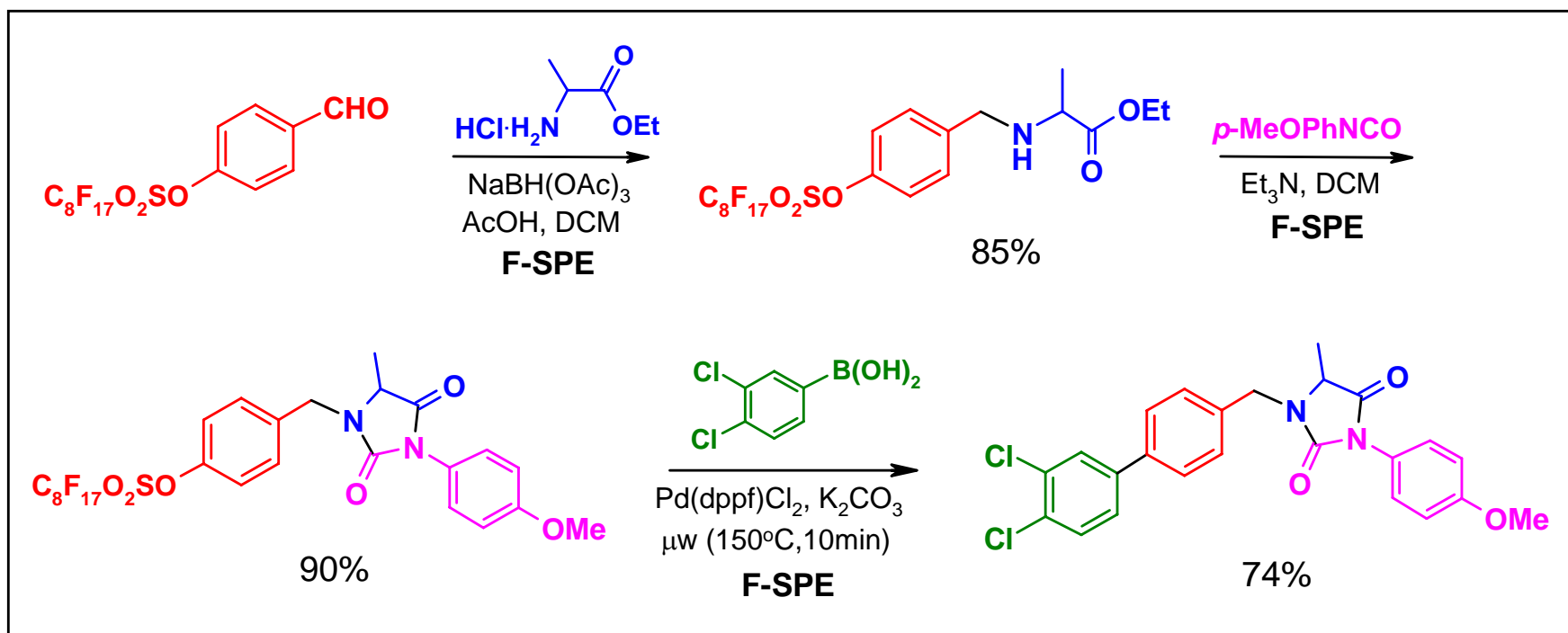
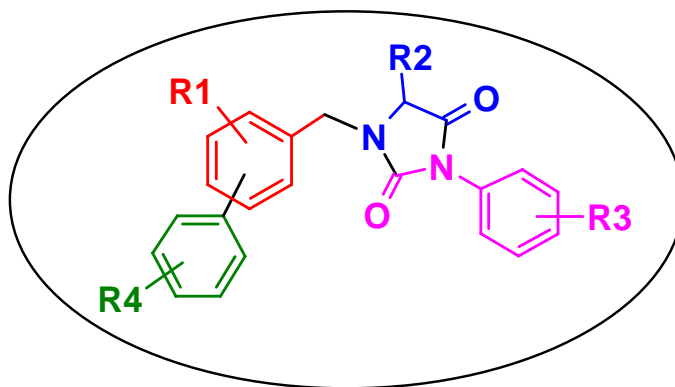
F-Benzaldehyde Protecting Group

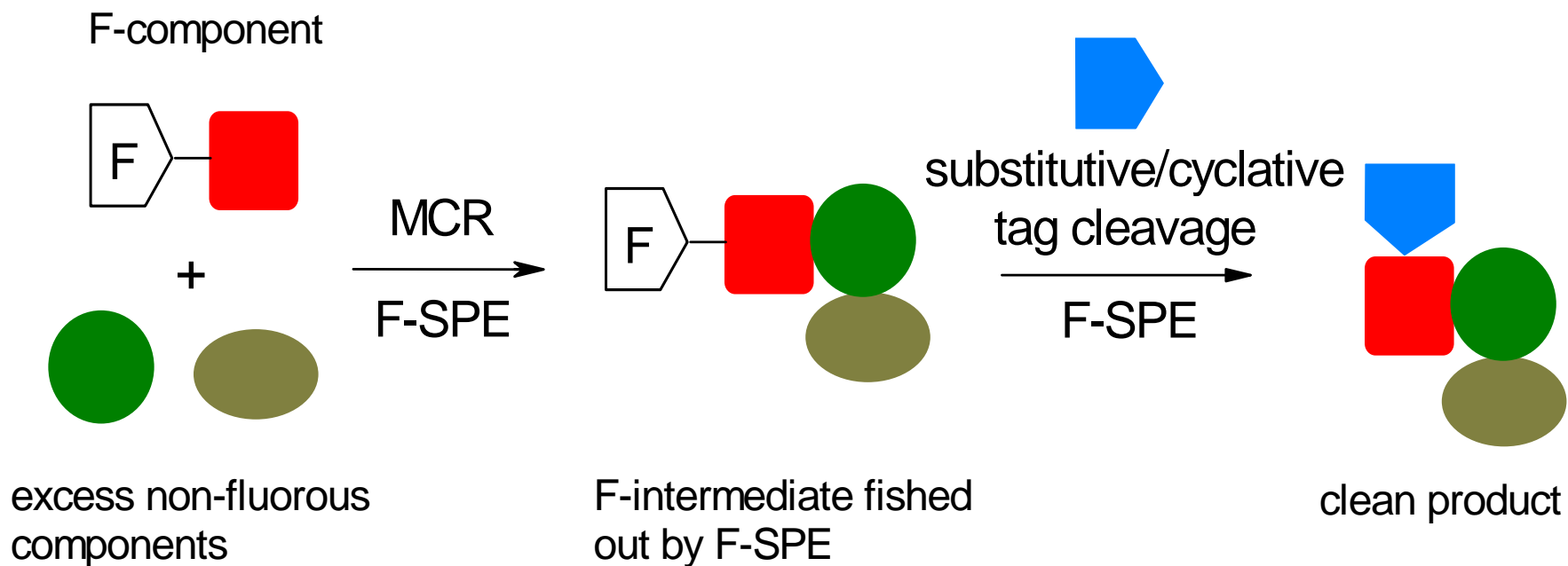


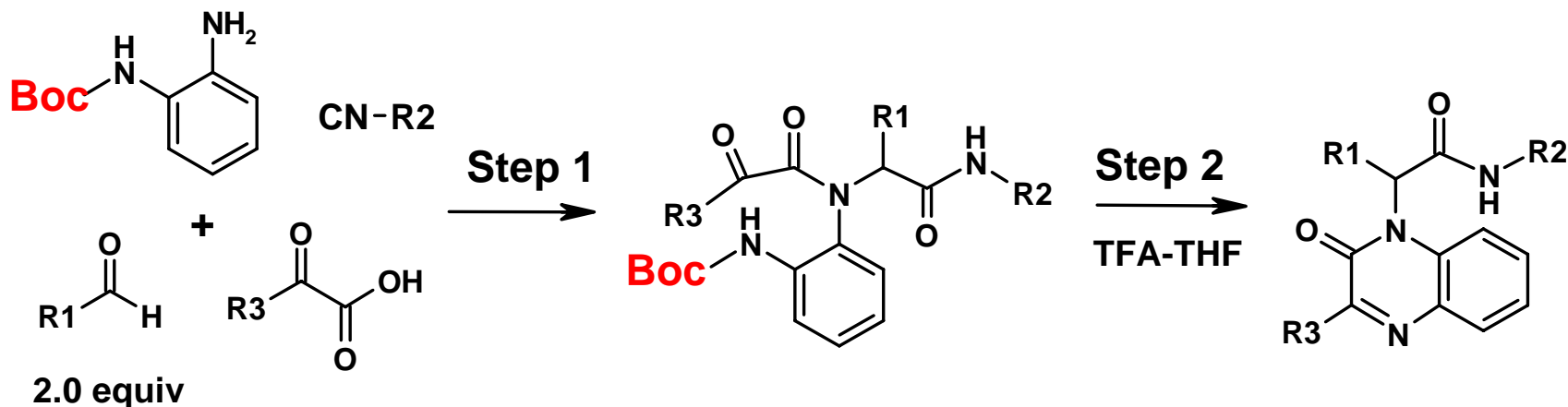
F-Sulfonates for Pd-catalyzed Couplings



Three functions of the fluorous tag: 1) OH protecting group; 2) F-tag for easy intermediate purification; 3) Activation of phenol for coupling







Step 1

normal Boc:¹ 36-48h, double scavenging
to remove aldehyde and acid

F-Boc + μW :² 120 °C, 20 min, F-SPE

Step 2

4-24 h, flash
chromatography

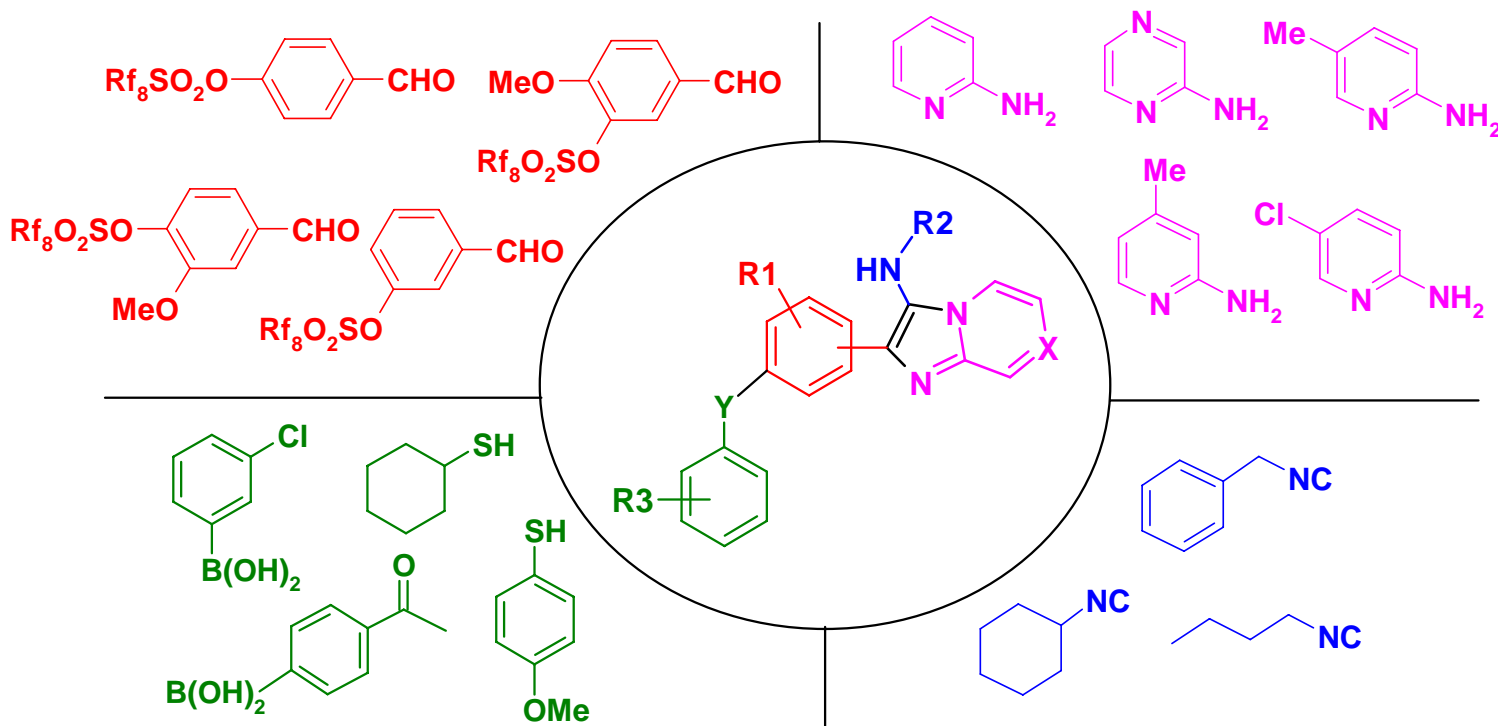
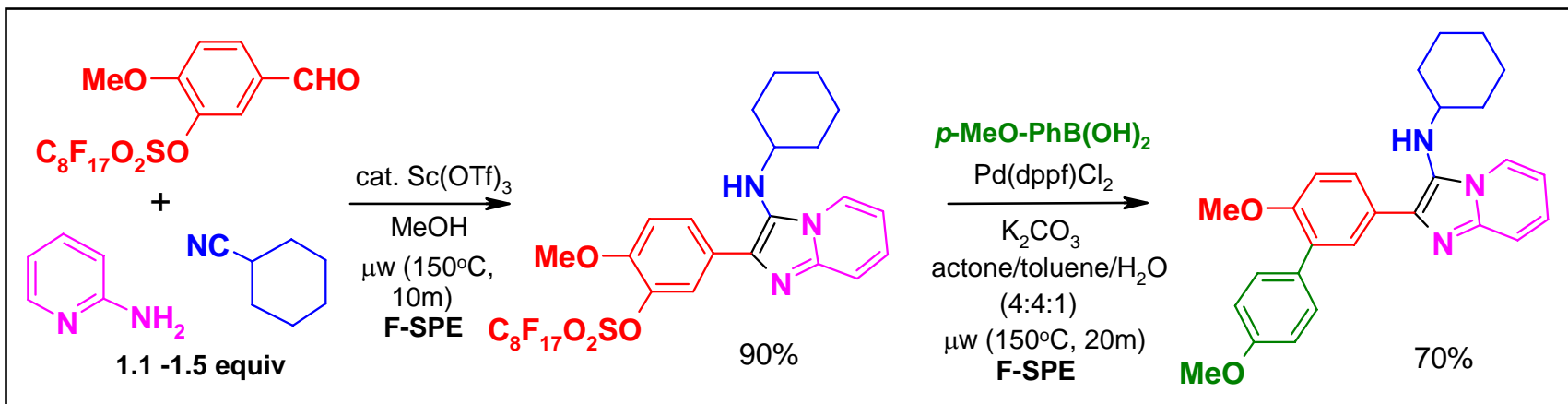
120 °C, 20 min, F-SPE

The microwave + fluorous approach is faster and easier

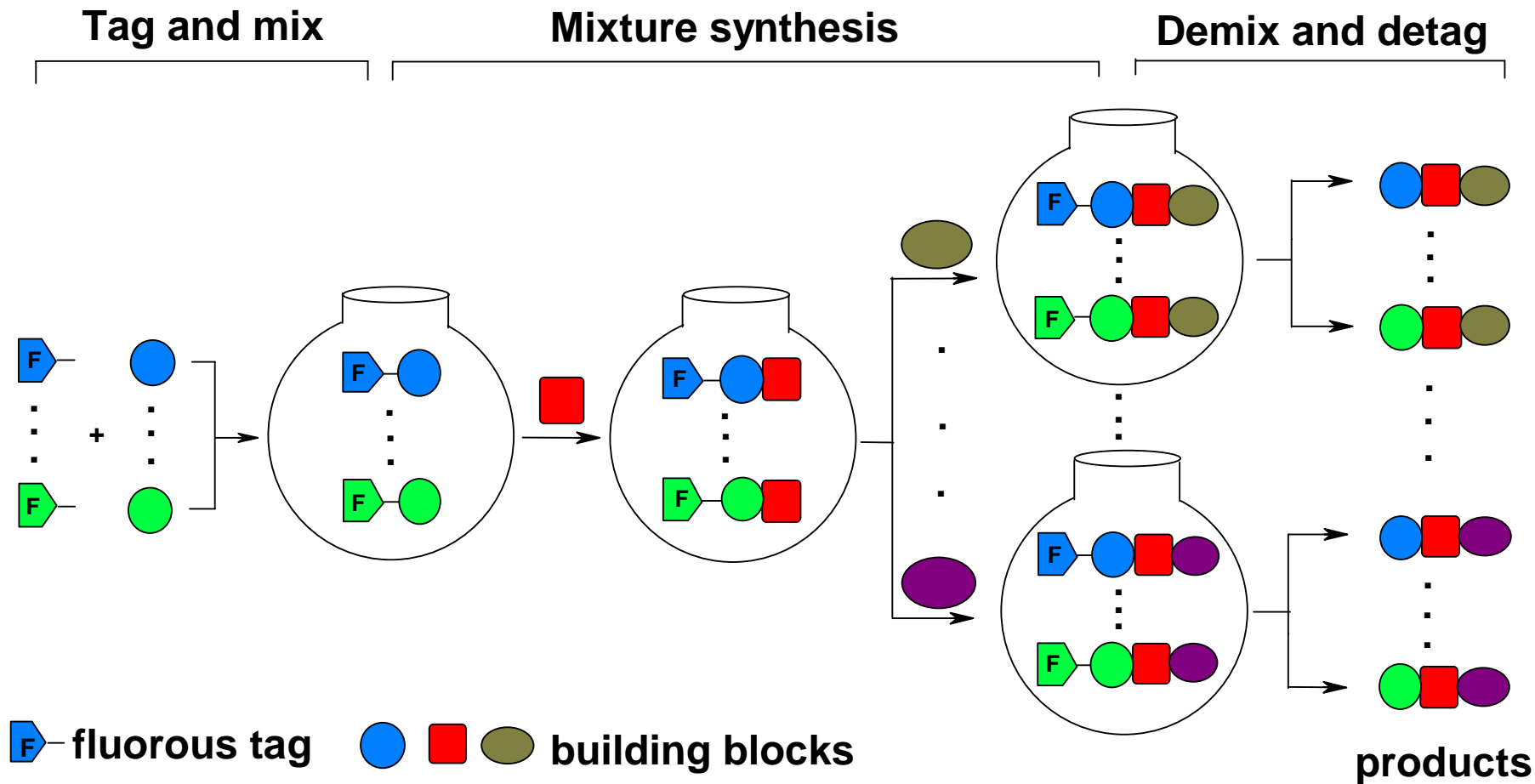
¹ Nixey, T.; Tempest, P.; Hulme, C. *Tetrahedron Lett.* **2002**, *43*, 1637.

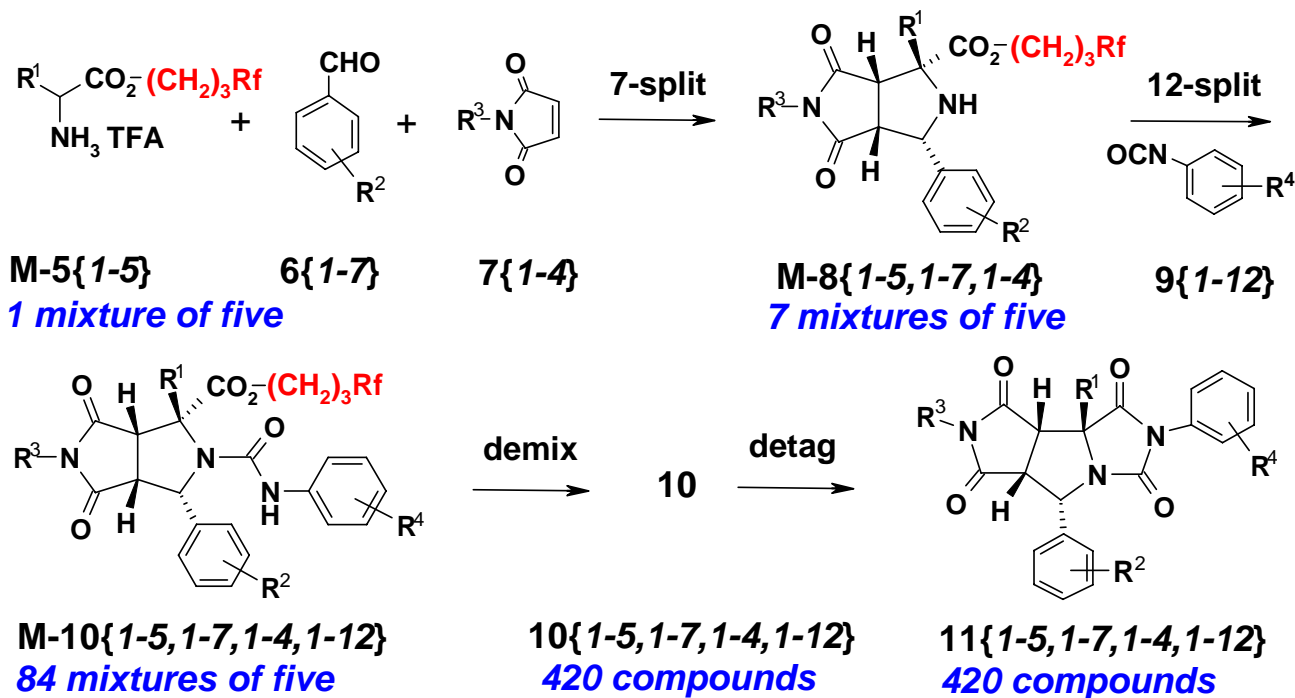
² Zhang, W.; Tempest, P. *Tetrahedron Lett.* **2004**, *45*, 6757.

Biaryl Substituted Imidazo[1,2-a]pyridines



Fluorous Mixture Synthesis (FMS)

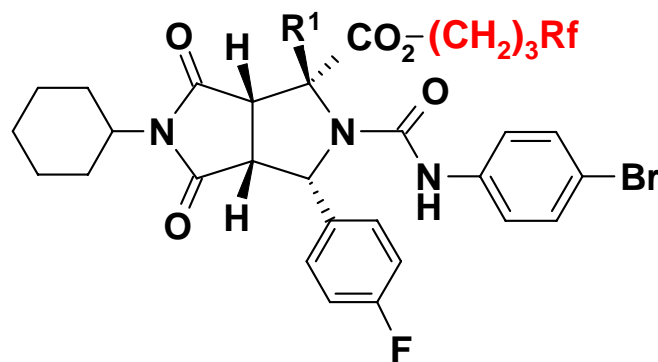




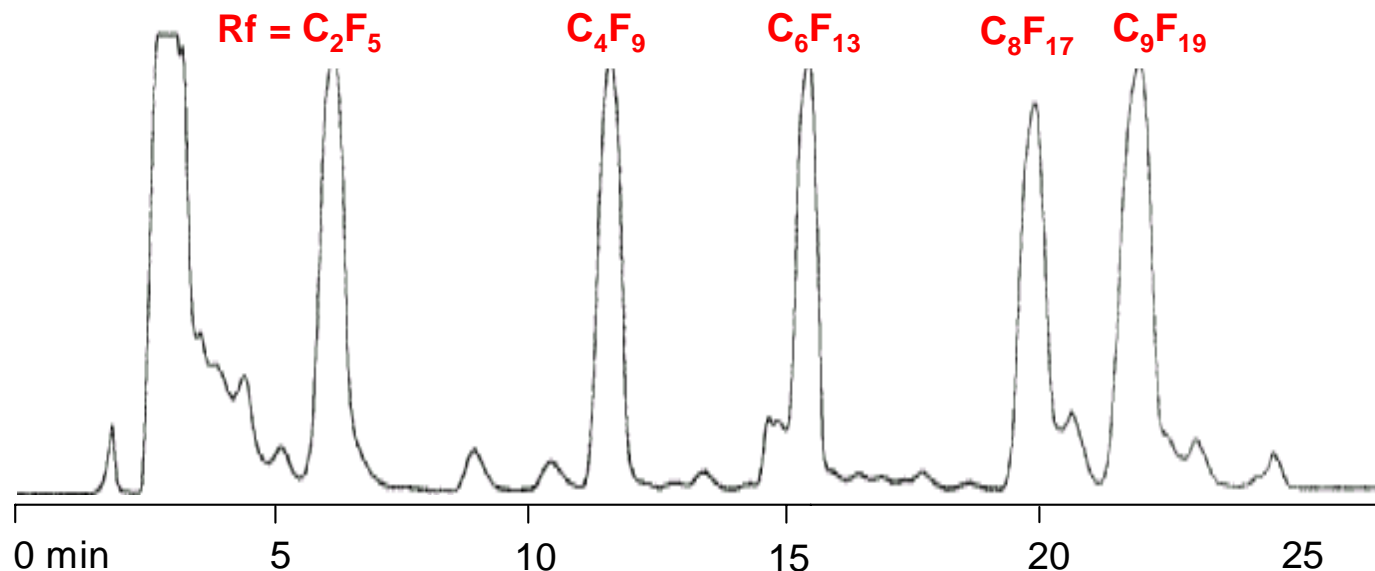
Rf/R ¹ {1-5}	R ² {1-7}	R ³ {1-4}	R ⁴ {1-12}
{1} C ₂ F ₅ /i-Bu	{1} H {5} <i>p</i> -F	{1} Et	{1} H {7} <i>p</i> -CF ₃
{2} C ₄ F ₉ /Bn	{2} <i>p</i> -Me {6} <i>p</i> -Cl	{2} <i>t</i> -Bu	{2} <i>p</i> -Me {8} 3,4-diCl
{3} C ₆ F ₁₃ / <i>p</i> -ClBn	{3} <i>p</i> -Br {7} <i>m</i> -Me	{3} <i>c</i> -C ₆ H ₁₁	{3} <i>p</i> -Br {9} <i>m</i> -Me
{4} C ₈ F ₁₇ /Me	{4} <i>p</i> -OMe	{4} Bn	{4} <i>p</i> -OMe {10} <i>m</i> -Br
{5} C ₉ F ₁₉ /Et			{5} <i>p</i> -F {11} <i>m</i> -F
			{6} <i>p</i> -Cl {12} <i>m</i> -Cl

420 Ureas M-10 (84 x 5) by **91 FMS reactions** (7 cycloaddition + 84 isocyanatereactions)
 Could need **455 parallel reactions** (35 cycloadditions + 420 isocyanate reactions)

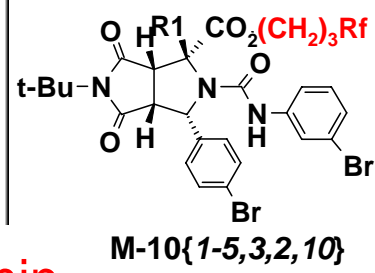
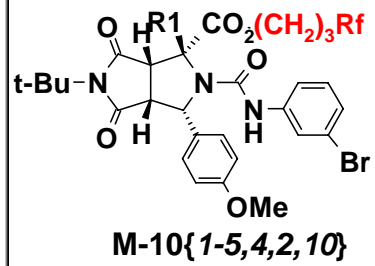
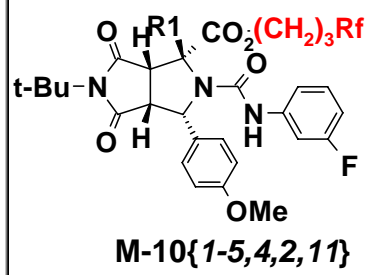
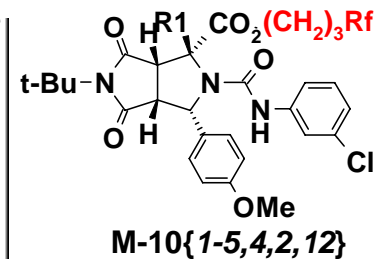
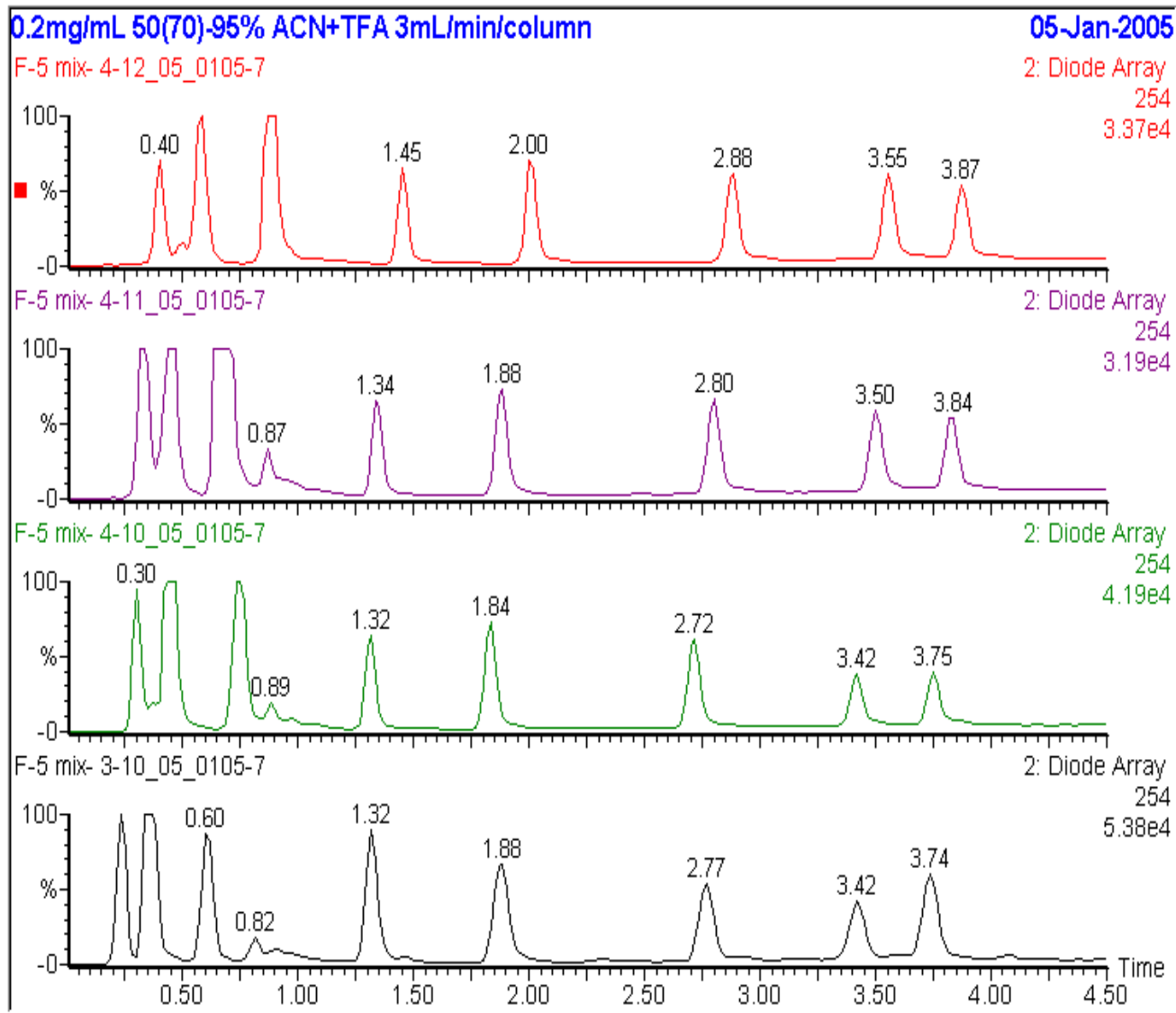
A Typical HPLC Demixing



M-10{1-5,5,3,3}



FluoroFlash® column (20x250 mm, 5 μ m), gradient 80:20 MeOH-H₂O to 100% MeOH in 23 min, then THF for 4 min, 20 mL/min.



Demixing and purification of **20 (4x5) compounds in 5 min**

Advantages of fluororous synthesis

- Homogeneous reaction
- Intermediate analysis/purification
- Selective orthogonal separation

Enhances existing technologies

- Microwave-assisted synthesis
- Multicomponent reactions
- Parallel and mixture synthesis
- Diversity-oriented synthesis
- SPE and chromatography
- Preparative parallel LC

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